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# Usefulness of Neutrophil-to-Lymphocyte Ratio in Risk Stratification of Patients With Advanced Heart Failure



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Elevated neutrophil-to-lymphocyte ratio (NLR) has been associated with increased mortality in patients with acute heart failure (HF) and neoplastic diseases. We investigated the association between NLR and mortality or cardiac transplantation in a retrospective cohort of 527 patients presented to the Cleveland Clinic for evaluation of advanced HF therapy options from 2007 to 2010. Patients were divided according to low, intermediate, and high tertiles of NLR and were followed longitudinally for time to all-cause mortality or heart transplantation (primary outcome). The median NLR was 3.9 (interquartile range 2.5 to 6.5). In univariate analysis, intermediate and highest tertiles of NLR had a higher risk than the lowest tertile for the primary outcome and all-causes mortality. Compared with the lowest tertile, there was no difference in the risk of heart transplantation for intermediate and high tertiles. In multivariate analysis, compared with the lowest tertile, the intermediate and high NLR tertiles remained significantly associated with the primary outcome (hazard ratio [HR] = 1.61, 95% confidence interval [CI] 1.10 to 2.37 and HR = 1.55, 95% CI 1.02 to 2.36, respectively) and all-cause mortality (HR = 1.83, 95% CI 1.07 to 3.14 and HR = 2.16, 95% CI 1.21 to 3.83, respectively). In conclusion, elevated NLR is associated with increased mortality or heart transplantation risk in patients with advanced HF. © 2015 Elsevier Inc. All rights reserved. (Am J Cardiol 2015;115:57–61)

Lymphocytopenia has long been associated with poor prognosis in heart failure (HF).<sup>1,2</sup> Several studies over the past few decades have demonstrated the potential of neutrophil-to-lymphocyte ratio (NLR), a widely available hematologic marker of oxidative stress damage, to serve as a good prognostic marker of mortality in cardiac and noncardiac diseases.<sup>3–7</sup> In this study, we evaluated the association between NLR and future risk of mortality or cardiac transplantation in a large contemporary cohort of patients with advanced HF.

## Methods

We analyzed 549 consecutive patients presented to the Cleveland Clinic (Cleveland, Ohio) from 2007 to 2010 for evaluation of advanced HF therapies and consideration for heart transplantation or mechanical circulatory assist

devices. Electronic medical records were used to obtain demographic variables (age, gender, and race), clinical variables, laboratory values, and medications. Among this cohort, 527 patients had documented values of NLR within the time frame and clinical stability to complete the comprehensive evaluation for advanced HF therapeutics and were included in this study. Mortality data were obtained from social security death index (until 2012) and timing of death and heart transplantation were confirmed by review of the electronic medical records. The construction of the database was conducted by an independent researcher who was not involved in the care of patients. Data were collected retrospectively and the study was approved by the Institutional Review Board of the Cleveland Clinic.

NLR was calculated as the ratio between neutrophil count and lymphocyte count obtained at the time of evaluation. Participants were categorized in NLR tertiles low (<3.0), intermediate (3.0 to 5.4), and high (>5.4). The primary outcome was a composite of all-cause mortality or heart transplantation. Information on heart transplantation was extracted from the electronic records.

Continuous variables were described as mean and SD or median with interquartile range. Categorical variables were expressed as frequencies and percentages. Continuous variables were compared among NLR tertiles with the analysis of variance or Kruskal-Wallis tests; categorical variables were compared with the chi-square test. The Kaplan-Meier method was used to evaluate survival or freedom from events, and the log-rank test was used to evaluate differences among NLR tertiles. Univariate and multivariate Cox regression models were used to assess the association between tertiles of NLR and the primary outcome or its components. We reported crude and adjusted hazard ratios

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See page 60 for disclosure information.

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Table 1  
Baseline characteristics of patients with severe chronic heart failure grouped in tertiles of neutrophil-to-lymphocyte ratio

Variable	Tertiles			p Value
	Low (n=176)	Intermediate (n=177)	High (n= 174)	
Age (years)	53 (43-61)	59 (51-64)	57 (47-64)	<0.01
Male	113 (64%)	136 (77%)	134 (77%)	<0.01
Black	42 (25.4%)	18 (11.2)	20 (12.7)	<0.01
Smoke	47 (27%)	35 (20%)	32 (18 %)	0.13
Diabetes mellitus	38(22%)	53(30%)	46 (26%)	0.19
Hypertension	60 (34%)	81(46%)	77 (44%)	0.05
Dyslipidemia	74(42%)	86(49%)	64 (37%)	0.07
Non-ischemic heart failure	113 (65%)	97 (55.4%)	100 (57.8%)	0.20
Chronic obstructive pulmonary disease	15(9%)	16 (9%)	14(8%)	0.98
Coronary Artery Disease	65 (37%)	77 (44%)	84 (48%)	0.10
Stroke	13 (7%)	21 (12%)	19 (11%)	0.33
Atrial Fibrillation	61(35%)	67(38%)	66 (38%)	0.76
Ventricular Assist Device	34 (19%)	58 (33%)	60 (35%)	<0.01
Creatinine (mg/dL) Estimated	1.1 (0.9-1.4)	1.2 (1.0-1.5)	1.3 (1.0-1.8)	<0.01
glomerular filtration rate (ml/min/1.73 m <sup>2</sup> )	85 (63-111)	81 (56-112)	68 (48-100)	<0.01
Total Protein (g/dL)	6.9 (6.3-7.4)	6.7 (6.2-7.3)	6.2 (5.3-6.9)	<0.01
Albumin (g/dL)	4.0 (3.6-4.4)	4.0 (3.4- 4.4)	3.4 (2.8-3.9)	<0.01
Bilirubin (mg/dL)	0.8 (0.5-1.2)	0.8 (0.5-1.5)	1.1 (0.7-1.8)	<0.01
Blood Urea Nitrogen (mg/dL)	20 (15-40)	24 (19-33)	29 (22-38)	<0.01
Sodium (mEq/L)	136 (134-139)	136 (134-139)	135(132-138)	<0.01
B-type Natriuretic Peptide (pg/mL)	454 (102-804)	498 (225-956)	619 (244-1224)	<0.01
Platelets (10 <sup>3</sup> /μL)	193 (155-244)	194 (164-231)	173 (127-223)	<0.01
Platelet to-lymphocyte ratio	104 (77-134)	157 (118-211)	222 (152-335)	<0.01
Mean Platelet Volume (fL)	10.5 (9.9-11.0)	10.4 (9.8-11.2)	10.2 (9.7-11.0)	0.21
Neutrophil-to-lymphocyte ratio	2.1 (1.6-2.5)	3.9 (3.4-4.8)	8.1 (6.5-12.4)	<0.01
Aspirin	94 (53%)	109 (62%)	94 (54%)	0.20
Beta-blocker	118 (67%)	130 (74%)	87 (50%)	<0.01
Angiotensin-converting enzyme Inhibitors	101 (57%)	80 (46%)	59 (34%)	<0.01
Clopidogrel	29(17%)	27(15%)	22 (13%)	0.60
Spiroglactone	85(48%)	90 (52%)	67 (39%)	0.05
Hydralazine	33 (19%)	50 (28%)	50 (29%)	0.05
Nitrate	46 (26%)	53 (30%)	56 (32%)	0.45
Angiotensin II receptor blocker	21(12%)	24 (14%)	16 (9%)	0.43
Warfarin	64 (36%)	63 (36%)	62 (36%)	0.99

Continuous variables are expressed as median (interquartile range).

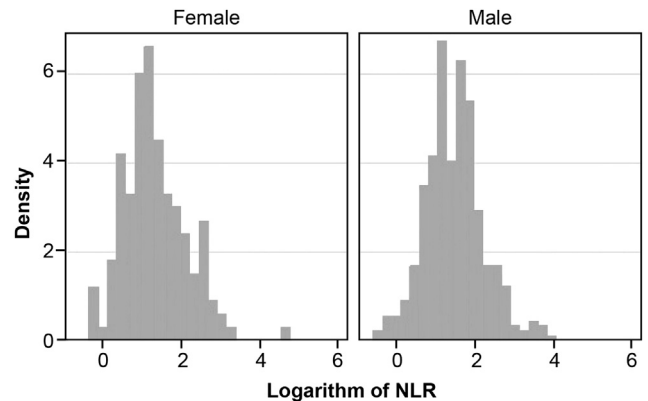
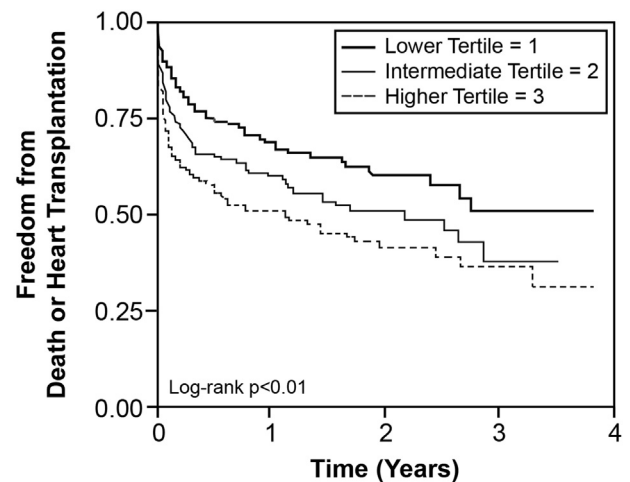


Figure 1. Distribution of NLR stratified according to gender.



Number at risk	Tertiles=1	Tertiles=2	Tertiles=3		
Tertiles=1	170	92	39	11	0
Tertiles=2	167	74	25	3	0
Tertiles=3	157	64	27	8	0

Figure 2. Kaplan-Meier curves comparing freedom from death or heart transplantation among NLR ratio tertiles in patients with advanced HF.

(HRs) with their 95% confidence intervals (CIs). Variables with  $p < 0.2$  in univariate analysis were considered candidates to enter into the multivariate model along with age, gender, and race. The variable mechanical circulatory assist device was analyzed as a time-dependent variable. Analyses were conducted in STATA version 11.0 (StataCorp LP, College Station, Texas).

## Results

Of the 527 patients, 176, 177, and 174 patients were in the lowest, intermediate, and higher NLR tertile, respectively. Baseline characteristics of the patients across NLR tertiles are listed in Table 1. Overall, NLR correlated directly with B-type natriuretic peptide ( $r = 0.14$ ,  $p < 0.01$ ). There was no correlation between NLR and left ventricular ejection fraction, peak oxygen consumption, and hemodynamic variables. The distribution of the logarithm of NLR is presented in Figure 1, stratified according to gender (mean  $\pm$  SD, NLR men  $5.9 \pm 6.3$  vs women  $5.5 \pm 8.4$ ,  $p = 0.6$ ).

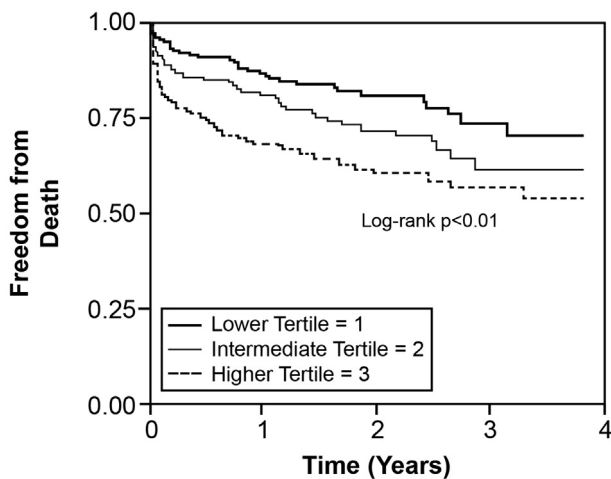
Table 2  
Univariate and multivariate Cox models for the primary and secondary outcomes

Outcomes	NLR Tertiles	Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
All-cause Mortality or Heart* Transplantation	Higher	1.93 (1.42-2.63)	<0.01	1.55 (1.02-2.36)	0.04
	Intermediate	1.42 (1.03-1.96)	0.03	1.61 (1.10-2.37)	0.02
	Lower	1	–	1	–
All-cause Mortality <sup>†</sup>	Higher	2.57 (1.72-3.85)	<0.01	2.16 (1.21-3.83)	<0.01
	Intermediate	1.56 (1.01-2.40)	0.04	1.83 (1.07-3.14)	0.03
	Lower	1	–	1	–
Heart Transplantation <sup>‡</sup>	Higher	1.05 (0.66-1.66)	0.84	0.80 (0.47-1.43)	0.43
	Intermediate	1.15 (0.74-1.76)	0.54	1.10 (0.68-1.84)	0.71
	Lower	1	–	1	–

\* Adjusted for: Age, sex, black race, cigarette smoker, diabetes, coronary artery disease, atrial fibrillation, ventricular assist device, albumin, bilirubin, blood urea nitrogen, sodium, brain natriuretic peptide, platelets, aspirin, beta-blocker, angiotensin-converting enzyme inhibitors and hydralazine.

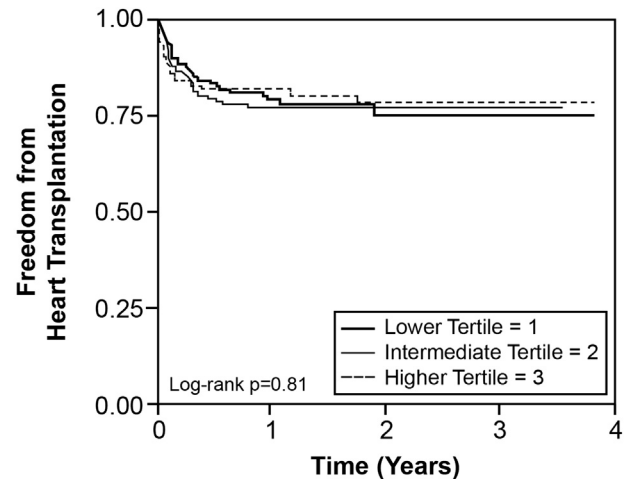
<sup>†</sup> Adjusted for: Age, sex, black race, diabetes, hypertension, No ischemic failure, chronic obstructive pulmonary disease, coronary artery disease, stroke, atrial fibrillation, ventricular assist device, creatinine, estimated glomerular filtration rate albumin, blood urea nitrogen, brain natriuretic peptide, platelets and beta-blocker.

<sup>‡</sup> Adjusted for: Age, black race, cigarette smoker, hypertension, dyslipidemia, no ischemic failure, chronic obstructive pulmonary disease, stroke, ventricular assist device, albumin, sodium, mean platelet volume, aspirin, beta-blocker, angiotensin-converting enzyme inhibitors and hydralazine. Model stratified by gender.



Number at risk	Tertiles=1	Tertiles=2	Tertiles=3
0	175	174	164
1	121	112	94
2	68	50	54
3	25	14	22
4	0	0	0

Figure 3. Kaplan-Meier curves comparing survival among NLR tertiles in patients with advanced HF.



Number at risk	Tertiles=1	Tertiles=2	Tertiles=3
0	171	169	166
1	94	85	70
2	40	27	28
3	11	3	8
4	0	0	0

Figure 4. Kaplan-Meier curves comparing freedom from heart transplantation among NLR tertiles in patients with advanced HF.

Over a median follow-up period of 11.3 (interquartile range 3.4 to 21.1) months, the primary outcome occurred in 263 patients (50%), 121 patients were transplanted (23%), and 158 patients died during follow-up (30%). In univariate analysis, NLR was associated with the primary end point ( $p < 0.01$ , Figure 2). In comparison to the lowest tertile, the intermediate and high tertiles of NLR had higher risk for the primary outcome. In multivariate analysis, and compared with the lowest tertile, the intermediate and highest NLR tertiles were associated with the primary outcome (HR = 1.61, 95% CI 1.10 to 2.37 and HR = 1.55, 95% CI 1.02 to 2.36, respectively; Table 2). Compared with the lowest tertile, the intermediate and highest tertiles of NLR had increased risk of all-cause mortality in univariate analysis (Figure 3). In multivariate analysis and compared with the

lowest tertile, the intermediate and high NLR tertiles remained significantly associated with all-causes mortality (HR = 1.83, 95% CI 1.07 to 3.14 and HR = 2.16, 95% CI 1.21 to 3.83, respectively; Table 2). No association between NLR and heart transplantation was observed in univariate analysis or multivariate analysis (Table 2, Figure 4). We did not find an association between lymphocyte or neutrophil counts with all-cause mortality in models using the same set of confounders of our primary analyses (Table 3).

## Discussion

The key finding of this analysis is that patients with advanced HF and higher levels of NLR portend higher mortality or heart transplantation risk. This association was

Table 3  
Multivariate Cox models for the primary and secondary outcomes and neutrophil and lymphocyte tertiles

Outcomes	Tertiles	Neutrophil Crude HR (95% CI)	Neutrophil Adjusted HR (95% CI)	p value	Lymphocyte Crude HR (95% CI)	Lymphocyte Adjusted HR (95% CI)	p value
All-cause Mortality or Heart Transplantation*	Higher	1.15 (0.83-1.60)	1.10 (0.74-1.62)	0.65	0.45 (0.33-0.62)	0.53 (0.35-0.81)	<0.01
	Intermediate	1.42 (1.05-1.94)	1.47 (1.04-2.08)	0.03	0.57 (0.42-0.77)	0.63 (0.44-0.90)	<0.01
	Lower	1	1	–	1	1	–
All-cause Mortality†	Higher	1.44 (0.97-2.14)	1.39 (0.84-2.31)	0.20	0.59 (0.39-0.88)	0.96 (0.54-1.69)	0.88
	Intermediate	1.16 (0.78-1.75)	1.05 (0.65-1.69)	0.85	0.68 (0.46-0.99)	0.96 (0.60-1.55)	0.87
	Lower	1	1	–	1	1	–
Heart Transplantation‡	Higher	0.67 (0.38-1.17)	0.56 (0.31-1.00)	0.05	0.46 (0.28-0.76)	0.45 (0.26-0.80)	<0.01
	Intermediate	1.59 (1.03- 2.47)	1.64 (1.04-2.58)	0.03	0.60 (0.38-0.94)	0.64 (0.33-0.87)	0.01
	Lower	1	1	–	1	1	–

\* Adjusted for: Age, sex, black race, cigarette smoker, diabetes, coronary artery disease, atrial fibrillation, ventricular assist device, albumin, bilirubin, blood urea nitrogen, sodium, brain natriuretic peptide, platelets, aspirin, beta-blocker, angiotensin-converting enzyme inhibitors and hydralazine.

† Adjusted for: Age, sex, black race, diabetes, hypertension, No ischemic failure, chronic obstructive pulmonary disease, coronary artery disease, stroke, atrial fibrillation, ventricular assist device, creatinine, estimated glomerular filtration rate albumin, blood urea nitrogen, brain natriuretic peptide, platelets and beta-blocker.

‡ Adjusted for: Age, black race, cigarette smoker, hypertension, dyslipidemia, no ischemic failure, chronic obstructive pulmonary disease, stroke, ventricular assist device, albumin, sodium, mean platelet volume, aspirin, beta-blocker, angiotensin-converting enzyme inhibitors and hydralazine. Model stratified by gender.

mainly driven by higher all-cause mortality risk, as we did not find association between NLR and heart transplantation after multivariate adjustments. Although NLR may link to mortality like several other conditions, the potential contributory role of NLR in disease progression is not supported by our analysis. Thus, it appears that NLR is more likely a risk marker than the altered composition of leukocytes being a risk mediator for advanced HF.

Several studies of NLR have been carried out in recent years in cardiac and noncardiac diseases.<sup>3,4</sup> NLR has been studied in acute coronary syndromes in which an increased risk of outcomes was observed in patients with higher values of NLR. Earlier studies in acute coronary syndromes suggested strong prognostic value of NLR associated with mortality risk,<sup>8–16</sup> whereas short- and long-term prognostic value also extended to those who underwent percutaneous coronary intervention.<sup>11,17–20</sup> Independently, either neutrophilia<sup>21,22</sup> or lymphopenia<sup>23,24</sup> have been associated with increased mortality in acute coronary syndromes and HF, respectively. Indeed, percent lymphocyte is an independent predictor of mortality in the Seattle Heart Failure Model.<sup>25,26</sup> Interestingly, NLR has been shown to be a better predictor of mortality than independent absolute neutrophil and lymphocyte counts in patients with acute decompensated HF.<sup>6</sup> There is still no consensus on the cut-off points to define the levels of NLR as most studies categorized into tertiles as we did in our study. In studies of acute cardiac diseases, the median values for the higher tertile of NLR ranged between 6 and 9, where the median of our higher tertile range was found.

Why is NLR a better marker of mortality than absolute lymphocyte and neutrophil count separately? We attribute the strength of the NLR to the fact that it combines 2 different immune pathways: neutrophils are involved with a much quicker response, whereas lymphocytes are related to more adaptive long-term response of the immune system, a synonymous of physiological stress.<sup>4</sup> Neutrophils produce the enzyme myeloperoxidase that is involved in

promoting phagocytic function of neutrophils, but when the levels of this enzyme are high, an excess of free radicals is produced that is responsible for tissue injury and elevated in HF.<sup>27</sup> As complete blood count is commonly ordered in patients with HF and often includes automated distributions of leukocyte subsets, the ability to risk stratify a patient population with advanced HF without additional testing is attractive.

Although ejection fraction, peak oxygen, and other hemodynamic variables are classic risk factors on mortality in HF,<sup>28,29</sup> we did not find associations of these variables with NLR. This may mean that the risk of death from NLR is independent of hemodynamic variables.

Our study has several limitations. First, only baseline measurements of NLR were available that made it impossible to evaluate NLR values over time and their effect on clinical outcomes. Second, we did not have information on exact causes of death, therefore we cannot further determine if inflammation is the primary driver of disease progression leading to mortality. Third, we did not have information on some potential confounders such as nutritional status or concomitant inflammatory conditions or acuity of disease; however, we had a large number of other relevant confounding variables that served for adjustment in multivariate models. Finally, this study was conducted at a single center with high expertise in the management of severe HF and our experience may not necessarily translate to those without our wide range of advanced therapeutic options.

## Disclosures

The authors have no conflicts of interest to disclose.

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